(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 April 2003 (24.04.2003)

PCT

(10) International Publication Number
WO 03/032951 A1

(51) International Patent Classification[7]: A61K 9/14, B01D 9/00, B01J 2/06

(21) International Application Number: PCT/US02/27444

(22) International Filing Date: 27 August 2002 (27.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/315,560 29 August 2001 (29.08.2001) US

(71) Applicant *(for all designated States except US)*: **DOW GLOBAL TECHNOLOGIES INC.** [US/US]; Washinton Street, 1790 Building, Midland, MI 48674 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HITT, James, E.** [US/US]; 2250 Cardinal, Midland, MI 48642 (US). **TUCKER, Christopher, J.** [US/US]; 5406 Wanetah, Midland, MI 48640 (US). **EVANS, Jonathan, C.** [US/US]; 4616 Congress Drive, Midland, MI 48642 (US). **CURTIS, Cathy, A.** [US/US]; 1609 Ohio Street, Midland, MI 48642 (US). **SVENSON, Sonke** [DE/US]; 2912 Canterbury, Midland, MI 48642 (US).

(74) Agent: **JOZWIAK, Elisabeth, T.**; The Dow Chemical Company, Intellectual Property, P.O. Box 1967, Midland, MI 48641-1967 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: A PROCESS FOR PREPARING CRYSTALLINE DRUG PARTICLES BY MEANS OF PRECIPITATION

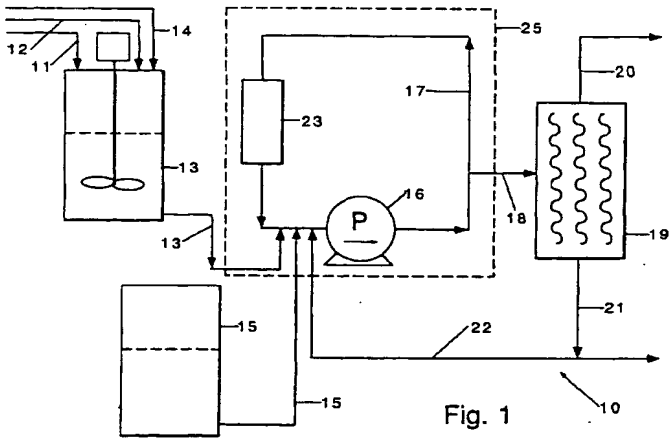

Fig. 1

(57) Abstract: A process for preparing crystalline particles of a drug substance is disclosed, said process comprising recirculating an anti-solvent through a mixing zone, dissolving the drug substance in a solvent to form a solution, adding the solution to the mixing zone to form a article slurry in the anti-solvent, and recirculating at least a portion of the particle slurry back through the mixing zone. Particles produced from the process are also disclosed. The present invention has the ability to be operated in a continuous fashion, resulting in a more efficient process and a more uniform product. The present invention has the additional advantage of having the ability to operate at a relatively low solvent ratio, thereby increasing the drug to excipient ratio.

WO 03/032951 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A PROCESS FOR PREPARING CRYSTALLINE DRUG PARTICULES BY MEANS OF PRECIPITATION

The present invention relates to drug particles and methods for their preparation. More particularly, the present invention relates to the preparation of drug particles utilizing a continuous solvent precipitation method.

High bioavailability and short dissolution times are desirable attributes of a pharmaceutical end product. Bioavailability is a term meaning the degree to which a pharmaceutical product, or drug, becomes available to the target tissue after being administered to the body. Poor bioavailability is a significant problem encountered in the development of pharmaceutical compositions, particularly those containing an active ingredient that is poorly soluble in water. Poorly water soluble drugs tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation.

It is known that the rate of dissolution of a particulate drug can increase with increasing surface area, such as by decreasing particle size. Furthermore, crystalline drug particles are desirable because of the greater stability as opposed to amorphous particles. Efforts have been made to control the size and morphology of drug particles in pharmaceutical compositions. The most commonly employed techniques involve precipitation of the drug substance. U.S. Patent 5,716,642 teaches the use of an acid-base precipitation method. However, the method described in the '642 patent results in a large concentration of salt which must be removed via dialysis in order to obtain relatively pure drug particles.

Solvent precipitation methods are described in U.S. Patent Nos. 4,826,689 and 6,221,398 B1, in Hasegawa et al, "Supersaturation Mechanism of Drugs from Solid Dispersions with Enteric Coating Agents, Chem. Pharm. Bull. Vol. 36, No. 12, p. 4941(1988), and Frederic Ruch and Egon Matijevic, Preparation of Micrometer Size Budesonide Particles by Precipitation, Journal of Colloid and Interface Science, 229, 207-211 (2000). In the standard method described in these references, a supersaturated solution of the compound to be crystallized is contacted with an appropriate 'anti-solvent' in a stirred vessel. Within the stirred vessel, the anti-solvent initiates primary nucleation which leads to crystal formation. However, the crystals that are formed are relatively large, whereas the smaller particles described by these references are amorphous. For the relatively large

crystalline particles, these methods almost always require a post-crystallization milling step in order to increase particle surface area and thereby improve their bioavailability. However, milling has drawbacks, including yield loss, noise and dust. Even wet milling techniques, as described in as described in U.S. Patent No. 5,145,684, exhibit problems associated with contamination from the grinding media. Moreover, exposing a drug substance to excessive mechanical shear or exceedingly high temperatures can cause the drug to lose its activity.

The precipitation methods described in the above-cited prior art also have the disadvantage of being operated in a batch fashion. Batch can be difficult to scale up to a commercial operation and are generally more inefficient than continuous processes. Moreover, a continuous process will often result in a more uniform product than a batch process.

U.S. Patent No. 5,314,506 describes a continuous crystallization method which utilizes impinging jets to mix two streams together in order to precipitate crystalline particles. The resulting particles are crystalline, but are relatively large. Moreover, the method of the '506 patent relies upon the momentum of the two streams to mix the two streams together, which can make operation on a large scale difficult. The '506 patent also results in mixing of the entire quantity of the two streams all at once rather than gradual addition of one stream to the other, which can be undesirable.

It would be an advantage in the art of direct preparation of crystalline drug particles to provide a method which is continuous and allows for scalability, which is applicable to a wide breadth of drug substances and which does not require the use of subsequent milling of the drug particles.

In one aspect, the present invention is a process for preparing crystalline particles of a drug substance comprising recirculating an anti-solvent through a mixing zone, dissolving the drug substance in a solvent to form a solution, adding the solution to the mixing zone to form a particle slurry in the anti-solvent, and recirculating at least a portion of the particle slurry back through the mixing zone.

In a second aspect, the present invention is drug particles prepared according to the process of recirculating an anti-solvent through a mixing zone, dissolving the drug substance in a solvent to form a solution, adding the solution to the mixing zone to form a particle

slurry in the anti-solvent, and recirculating at least a portion of the particle slurry back through the mixing zone.

The present invention has the advantage of being a continuous process, resulting in a more efficient process and a more uniform product. The present invention has the additional advantage of having the ability to operate at a relatively low solvent ratio and increasing the drug level in the particle slurry, thereby increasing the drug to excipient ratio.

FIG. 1 is a schematic diagram illustrating the process of the present invention.

Figure 1 is a schematic diagram illustrating one embodiment of the continuous process 10 of the present invention. A drug substance 11 is mixed with an organic solvent 12 to form a solution 13.

The drug substance 11 which can be used in the process of the present invention can be any poorly water soluble drug. Suitable drug substances can be selected from a variety of known classes of drugs including, for example, analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiacinotropic agents, contrast media, corticosterioids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasidilators and xanthines. Preferred drug substances include those intended for oral administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989.

The organic solvent 12 into which the drug is dissolved can be any organic solvent which dissolves the drug adequately. Generally, the higher the solubility of the drug in the solvent, the more efficient the process will be. The solvent should be miscible in anti-solvent.

Preferably, the selected solvent exhibits ideal mixing behavior with anti-solvent so that the solution can be instantaneously distributed throughout the particle slurry, as described hereinbelow. Suitable organic solvents include but are not limited to methanol, ethanol, isopropanol, 1-butanol, trifluoroethanol, polyhydric alcohols such as propylene glycol, PEG 400, and 1,3-propanediol, amides such as n-methyl pyrrolidone, n,n-dimethylformamide, tetrahydrofuran, propionaldehyde, acetone, n-propylamine, isopropylamine, ethylene diamine, acetonitrile, methyl ethyl ketone, acetic acid, formic acid, dimethylsulfoxide, 1,3-dioxolane, hexafluoroisopropanol, and combinations thereof.

The concentration of drug in the solution is preferably as close as practical to the solubility limit of the solvent. Such concentration will depend upon the selected drug and solvent but is typically in the range of from 0.1 to 20.0 weight percent.

Optionally, one or more stabilizers 14 can be introduced into the solution 13. Stabilization is defined herein to mean that the resulting drug particles do not grow substantially, such that particles prepared from precipitation in the presence of stabilizer are generally smaller than those prepared without a stabilizer. Stabilization should be carried out in such a way that addition of additional drug solution substantially results in new particle formation and not growth of existing particles.

The choice of stabilizer or stabilizers will depend upon the drug molecule. Generally, polymeric stabilizers are preferred. Examples of particle stabilizers include phospholipids, surfactants, polymeric surfactants, vesicles, polymers, including copolymers and homopolymers and biopolymers, and/or dispersion aids. Suitable surfactants include gelatin, casein, lecithin, phosphatides, gum acacia, cholesterol, tragacanth, fatty acids and fatty acid salts, benzalkonium chloride, glycerol mono and di fatty acid esters and ethers, cetostearyl alcohol, cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, for example, the commercially available Tweens, polyethylene glycols, poly(ethylene oxide/propylene oxide) copolymers, for example, the commercially available Poloxomers or Pluronics, polyoxyethylene fatty acid ethers, for example, the commercially available Brijs, polyoxyethylene fatty acid esters, sorbitan fatty acid esters, for example, the commercially available Spans, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, noncrystalline

cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), sodium lauryl sulfate, polyvinylpyrrolidone (PVP), poly(acrylic acid), and other anionic, cationic, zwitterionc and nonionic surfactants. Other suitable stabilizers are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. Such stabilizers are commercially available and/or can be prepared by techniques known in the art.

An important part of the continuous process of the present invention is the use of a mixing zone 25. Utilization of the mixing zone results in high velocity, high turbulence, efficient heat exchange in a form that is easily scalable. In the embodiment shown in Figure 1, mixing zone 25 comprises pump 16 together with recirculation loop 17.

Anti-solvent 15 is pumped by way of pump 16 through the recirculation loop 17. The term "anti-solvent" is defined as any material in which the drug is poorly soluble, defined as meaning less than 10 mg/ml. Water is the preferred anti-solvent. In one embodiment, the anti-solvent contains one or more stabilizers, such as those stabilizers described above.

The solution 13 is then added to the anti-solvent in the mixing zone 25 to form a slurry of drug particles in anti-solvent, referred to herein as a particle slurry. As the solution is added to the anti-solvent in the mixing zone, the resulting particle slurry is mixed. Any external device which imparts intense mixing of the particle slurry in the mixing zone 25 can be used, as long as the selected device will permit continuous operation. "Intense mixing" is defined herein as meaning that a uniformly supersaturated particle slurry is formed prior to new particle nucleation. The mixing should be sufficiently intense so as to result in nearly instantaneous dispersion of the solution across the particle slurry before new particle growth occurs. As with stabilization, mixing should be carried out in such a way that addition of additional drug solution substantially results in new particle formation and does not substantially result in growth of existing particles. Such intense mixing results in supersaturation of the drug substance in the slurry, causing drug particles to precipitate into small particles having a crystalline structure. If stabilization fails, growth on existing particles predominates over new particle formation, resulting in large crystals which may require milling to meet bioavailability requirements.

Advantageously, steady-state conditions can be approached gradually using the process of the present invention, rather than all at once. In the embodiment shown in Figure 1, which contains loop 17 in combination with pump 16, preferably, the combination of steady-state flow rate, anti-solvent fluid properties, and line diameter in loop 17 are sufficient to achieve a Reynolds number of at least 2500, more preferably at least 5000, even more preferably at least 10,000 in the loop 17. The drug solution can be added to the mixing zone slowly or quickly as desired. The rate of addition of drug solution is not critical, so long as the relative flow rates of the solution and the particle slurry are sufficient to create intense mixing. For example, for the embodiment shown in Figure 1, the rate of addition of the drug solution can be about (0.6 x V)/minute wherein V is the volume of the mixing zone.

Examples of devices which may be used to mix the two streams in the mixing zone include one or more of a centrifugal pump, an in-line homogenizer, an ultrasonic mixer, an atomizer, and a colloid mill. Combinations of such mixing devices may also be used, especially in those cases where it is desirable to increase residence time in the mixing zone. In the embodiment illustrated in Figure 1, centrifugal pump 16 together with a recirculation loop 17 serves as a mixing device.

The particle slurry will contain new drug particles that are continuously being formed by precipitation, as well as existing drug particles that have previously been formed and recirculated and have been stabilized to substantially prevent further growth. Desirably, the concentration of drug in the particle slurry can gradually increase as steady-state conditions are approached. Once steady-state is reached, it is desirable to have the drug concentration as high as is practical. A high drug concentration is an advantage of the present invention, because with a high drug concentration, the quantity of stabilizer is efficiently utilized, leading to a relatively low quantity of stabilizer relative to the drug. Preferably, the drug concentration is at least 0.01 weight percent, more preferably at least 0.1 weight percent and even more preferably at least 0.5 weight percent at equilibrium.

Optionally, one or more stabilizers may be added to the anti-solvent. Suitable particle stabilizers include those listed above for inclusion in the solution. The particular stabilizer or stabilizers selected for use in the anti-solvent can be the same or can be different from the stabilizer(s) in the solution. The weight ratio of drug to total stabilizer in the particle slurry is from 0.1:1 to 10:1.

Advantageously, additional excipients can be added to either the solution or to the anti-solvent, either before or after the drug particles are formed, in order to enable the drug particles to be homogeneously admixed for appropriate administration. Suitable excipients include polymers, absorption enhancers, solubility enhancing agents, dissolution rate enhancing agents, bioadhesive agents, and controlled release agents. More particularly, suitable excipients include cellulose ethers, acrylic acid polymers, and bile salts. Other suitable excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. Such excipients are commercially available and/or can be prepared by techniques known in the art.

In a preferred embodiment, the particle slurry is recycled back through the mixing zone. The particle slurry in the mixing zone is controlled at a reduced temperature by way of heat exchanger 23. Preferably, the temperature of the particle slurry in the mixing zone is controlled at less than 65 °C, more preferably less than 30 °C, even more preferably less than 23 °C, and most preferably less than 10 °C. The lower limit of the temperature of the particle slurry is the freezing point of the anti-solvent, or 0 °C if the anti-solvent is water. Temperatures which are too high could lead to undesirable particle growth.

Once the particle slurry has recirculated at reduced temperature and the solution has been introduced, equilibrium conditions can be achieved. In a preferred embodiment, anti-solvent feed line 15 will act as a anti-solvent make-up line to make up for any anti-solvent lost in the process.

An optional slip stream 18 continuously permits at least a portion of the particle slurry to be fed to solvent removal step. Any solvent removal operation can be used, including membrane filtration, diafiltration and evaporation. In the embodiment illustrated in Figure 1, an evaporator 19 is shown. Any appropriate evaporator can be used, as long as it permits continuous operation and evaporates a substantial quantity of solvent 20, leaving drug particles suspended in anti-solvent, referred to herein as a stripped slurry 21. Examples of evaporators include a falling film evaporator and a wiped film evaporator. A wiped film evaporator is preferred, because such an evaporator helps to reduce any foaming that might occur during processing. The wiped film evaporator can be arranged either horizontally or vertically. The operating conditions of the evaporator will depend upon the solvent used.

Preferably, the evaporator is held under vacuum and is operated at a temperature at least as high as the boiling point of the solvent.

In a preferred embodiment, the process of the present invention includes the step of passing at least a portion 22 of the stripped slurry back through the mixing zone 25. Advantageously, this step results in a higher drug particle concentration in the recirculated particle slurry and a lower solvent concentration, which in turn results in more efficient drug particle recovery and a higher drug to stabilizer ratio. Additionally, a lower solvent concentration results in generally lower particle size because solvent is not as available to facilitate drug migration and particle growth.

The resulting drug particles that are present in the stripped slurry are formed directly, without the need for subsequent milling. The drug particles in the stripped slurry preferably have a mean volume average particle size, without filtration, of less than 5 microns, more preferably less than 2 microns, and even more preferably less than 1 micron. The resulting drug particles are substantially crystalline in nature.

The process of the present invention desirably further comprises the step of recovering the drug particles. In one embodiment, recovering the drug particles comprises removing the anti-solvent from the particles. The anti-solvent can be removed directly after the particle slurry is formed, or the anti-solvent can be removed after any residual solvent is evaporated from the particle slurry. The choice will depend upon the concentration of solvent in the particle slurry and the chosen method to remove the anti-solvent. Removing the anti-solvent can be performed using any desirable means, including spray drying, spray freezing, gellation, (defined as gelling the particles with a polymer), lyophilization, or filtration.

The resulting drug particles are desirably redispersible in the anti-solvent with nearly the same particle size as the particles in the stripped slurry. Preferably, the mean particle size in the redispersed drug particles is within 60 percent of the particle size in the stripped slurry, more preferably within 50 percent, even more preferably within 30 percent, and yet even more preferably within 20 percent.

The following examples are for illustrative purposes only and are not intended to limit the scope of the claimed invention. Percentages are in weight percents unless otherwise stated.

Examples

Examples 1 through 3

A continuous precipitation process shown in Figure 1 was used. 150 grams of deionized water was recirculated using centrifugal pump (Cole- Parmer Model 75225-10) at maximum pump speed through recirculation loop 17 and through heat exchanger 23 (Exergy Inc. Model 00283-01, 23 series heat exchanger) until the temperature reached 5 °C. 30.8 grams of a solution of 5 wt percent Danazol and 2.5 wt percent Pluronic F-127 in methanol was added into the water over about 25 seconds. A particle slurry was formed. The particle size of the particle slurry was measured, without filtration, using a Coulter LS 230 and is listed in Table I below. The particle slurry was then fed to a wiped film evaporator having a jacket temperature of 40 °C, an absolute pressure of 10.5 mm Hg, and a feed rate of 10 mL/min. The particle size of the stripped slurry was measured, without filtration, using a Coulter LS 230 and is listed in Table I below. The stripped slurry was then fed back to the recirculation loop, with sufficient water being used to bring the total to about 150 grams. This precipitation procedure was repeated two more times using the amounts of materials listed in Table I, each repetition corresponding to examples 2 and 3, respectively.

Example 4

After the third pass through the recirculation loop and the wiped film evaporator, the stripped slurry was sent back through the wiped film evaporator for a second pass. The wiped film evaporator had a jacket temperature of 40 °C, an absolute pressure of 10.5 mm Hg and a feed rate of 10 mL/min. The final slurry weight and particle size are listed in Table I.

Table I

Example	Deionized Water (grams)	Danazol Solution (grams)	Final weight after evaporation (grams)	Mean volume average particle size (μm)	
				Before evaporation	After evaporation
1	150.0	30.8	96.7	0.156	--
2	65.9	30.2	94.6	0.219	0.242
3	59.5	30.9	98.2	0.277	0.307
4	0	0	60.4	0.307	0.322

Example 5

The stripped slurry from Example 4 was freeze dried 48 hours in a VirTis freeze dryer (catalog number 6201 3150) with an Edwards vacuum pump operated at maximum vacuum to isolate the drug particles. The drug particles were reconstituted by mixing with deionized water to a level of 1-2 wt percent solids and shaking by hand. The mean volume average particle size of the reconstituted freeze dried drug particles was 0.489 um, as measured, without filtration, using a Coulter LS 230.

Examples 6-8

A continuous process shown in Figure 1 was used, except that the stabilizer was added to the anti-solvent rather than to the solution. 150.1 grams of deionized water containing 3.0 wt percent polyvinylpyrrolidone (55,000 molecular weight, Aldrich) was recirculated using a centrifugal pump (Cole- Parmer Model 75225-10) at maximum pump speed through recirculation loop 17 and heat exchanger 23 (Exergy Inc. Model 00283-01, 23 series heat exchanger) until the temperature reached 3 °C. 29.92 grams of a solution of 6.67 wt percent Naproxen in methanol was added into the water over about 25 seconds to form a particle slurry. A sample of the particle slurry was taken, and the particle size of the sample was measured, without filtration, using a Coulter LS 230. A portion of the particle slurry was removed (15-20 percent). The amount of particle slurry recycled from the previous example is listed in Table II. Additional Naproxen in methanol solution was then added into the particle slurry over about 25 seconds. This was repeated once more. Table II lists the amount of Naproxen solution added and the resulting particle sizes for all three of Examples 6-8.

Table II

Example	Deionized Water/PVP (grams)	Naproxen Solution (grams)	Particle slurry recycled from previous example (grams)	percent Naproxen of total solids	Mean volume average particle size (μm)
6	150.1	29.92	--	30.7	0.230
7	0	25.12	150.44	47.0	0.373
8	0	20.83	145.68	57.1	0.414

Example 9-11

A continuous process shown in Figure 1 was used, except that the stabilizer was added to the anti-solvent rather than to the solution. These examples demonstrated recycling at least a portion 22 of the stripped slurry back through recirculation loop 17. 150.39 grams of deionized water containing 3.0 wt percent polyvinylpyrrolidone (55,000 molecular weight, Aldrich) was recirculated using a centrifugal pump (Cole- Parmer Model 75225-10) at maximum pump speed through recirculation loop 17 and heat exchanger 23 (Exergy Inc. Model 00283-01, 23 series heat exchanger) until the temperature reached 3 °C. 30.10 grams of a solution of 6.67 wt percent Naproxen in methanol was added into the water over about 25 seconds to form a particle slurry. The particle slurry was then fed to a wiped film evaporator operating at 22-25 mm Hg absolute pressure and 30-40 °C jacket temperature to strip most of the solvent. Sufficient water was added to the stripped slurry to bring the total slurry to about 150 grams, and the entire quantity was then fed back through the recirculation loop 17. Additional Naproxen/methanol solution was then added to the recirculation loop, and the slurry was then sampled for particle size. The particle size of the stripped slurry was measured, without filtration, using a Coulter LS230. Table III lists the amount of water added to the slurry, the Naproxen solution added, and the resulting particle sizes for all three of Examples 9-11.

Table III

Example	Deionized Water/PVP (grams)	Naproxen Solution (grams)	Stripped slurry from previous example (grams)	Percent Naproxen of total solids	Mean volume average particle size (μm)
9	150.39	30.10	--	30.8	--
10	13.95*	30.13	137.24	47.1	0.304
11	27.36*	30.01	128.85	57.1	0.299

* Deionized water containing no PVP.

Examples 12 through 17

A continuous precipitation process shown in Figure 1 was used. 150.14 grams of deionized water containing 2.5 wt percent polyvinylpyrolidone (55,000 molecular weight, Aldrich) was recirculated using centrifugal pump (Cole- Parmer Model 75225-10) at maximum pump speed through recirculation loop 17 and through heat exchanger 23 (Exergy

Inc. Model 00283-01, 23 series heat exchanger) until the temperature reached 3-4 °C. 30.06 grams of a solution of 7 wt percent Naproxen in methanol solution was added into the water over about 25 seconds to form a particle slurry. The particle slurry was then fed to a wiped film evaporator having a jacket temperature of 26-28 °C, an absolute pressure of 5-6 mm Hg, and a feed rate of about 15 mL/min. The particle size of the stripped slurry was measured, without filtration, using a Coulter LS 230 and is listed in Table IV below. Half of the stripped slurry was collected for isolation and the other half was then fed back to the recirculation loop, with sufficient water being used to bring the total to about 75 grams. About 75 grams of deionized water containing 2.5 wt percent polyvinylpyrolidone (55,000 molecular weight, Aldrich) was added to the recirculation loop to make up for the polymer collected in the isolation stream. This precipitation procedure was repeated five more times using the amounts of materials listed in Table IV, each repetition corresponding to examples 13 through 17, respectively.

Table IV

Example	2.5 wt percent PVP in water (grams)	De-ionized Water (grams)	Re-cycled particle slurry (grams)	Naproxen Solution (grams)	Final weight after evaporation (grams)	Isolation particle slurry (grams)	Mean volume average particle size after evaporation (μm)
12	150.14	0	0	30.06	120.30	60.00	0.361
13	75.11*	14.75	60.30	29.86	66.01	31.14	0.382
14	75.15*	40.41	31.14	29.53	133.77	66.39	0.292
15	76.48	7.82	66.39	30.07	137.85	68.07	0.292
16	75.35	6.89	68.07	30.02	110.72	55.74	0.347
17	75.87	21.14	55.74	29.99	124.54	124.54	0.392

* 1.25 wt percent PVP was used for these examples.

WHAT IS CLAIMED IS:

1. A process for preparing crystalline particles of a drug substance comprising:

recirculating an anti-solvent through a mixing zone;

dissolving the drug substance in a solvent to form a solution;

adding the solution to the mixing zone to form a particle slurry in the anti-solvent; and

recirculating at least a portion of the particle slurry back through the mixing zone.

2. The process according to Claim 1 further comprising:

removing the solvent from the particle slurry to form a stripped slurry.

3. The process according to Claim 2 further comprising:

recycling a portion of the stripped slurry back through the mixing zone.

4. The process according to Claim 1 wherein the temperature of the mixing zone is from 0 to 65 ° C.

5. The process according to Claim 1 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, 1-butanol, trifluoroethanol, polyhydric alcohols, amides, tetrahydrofuran, propionaldehyde, acetone, n-propylamine, isopropylamine, ethylene diamine, acetonitrile, methyl ethyl ketone, acetic acid, formic acid, dimethylsulfoxide, 1,3-dioxolane, hexafluoroisopropanol, and combinations thereof.

6. The process according to Claim 1 wherein the concentration of drug substance in the solution is from 0.1 to 20.0 weight percent.

7. The process according to Claim 1 wherein at least one stabilizer is added to the solution, to the anti-solvent or to both the solution and the anti-solvent.

8. The process according to Claim 7 wherein the stabilizer or stabilizers are polymeric stabilizers.

9. The process according to Claim 7 wherein the weight ratio of drug to total stabilizer in the particle slurry is from 0.1:1 to 10:1.

10. The process according to Claim 1 wherein the mixing zone comprises a mixer.

11. The process according to Claim 10 wherein the mixer is selected from the group consisting of a centrifugal pump, a recirculation loop, an in-line homogenizer, an ultrasonic mixer, an atomizer, a colloid mill and a combination thereof.

12. The process according to Claim 1 further comprising the step of removing the anti-solvent from at least a portion of the particle slurry.

13. The process according to Claim 12 wherein the anti-solvent is removed by way of spray drying, spray freezing, gellation, lyophilization, or filtration.

14. The process according to Claim 2 wherein the removing of the solvent comprises using membrane filtration, diafiltration, or evaporation.

15. The process according to Claim 14 wherein the removing of the solvent occurs using a wiped film evaporator.

16. The process according to Claim 2 further comprising the step of removing the anti-solvent from at least a portion of the stripped slurry.

17. The process according to Claim 16 wherein the anti-solvent is removed by way of spray drying, spray freezing, gellation, lyophilization, or filtration.

18. Drug particles prepared according to the process of Claim 1.

19. Drug particles according to Claim 18, wherein the process further comprises the step of removing the solvent from the particle slurry to form a stripped slurry.

20. Drug particles according to Claim 19, wherein the process further comprises the step of recycling a portion of the stripped slurry back through the mixing zone.

21. Drug particles according to Claim 18, wherein the process further comprises the step of removing the anti-solvent from the particle slurry.

22. Drug particles according to Claim 20, wherein the process further comprises the step of removing the anti-solvent from the stripped slurry.

23. Drug particles according to Claim 22, wherein the drug particles are redispersible in anti-solvent and maintain a mean particle size within 60 percent of the particle size in the stripped slurry when redispersed in anti-solvent.

24. Drug particles according to Claim 18, having a mean particle size of less than about 5 microns.

25. Drug particles according to Claim 24 having a mean particle size of less than 2 microns.

1 / 1

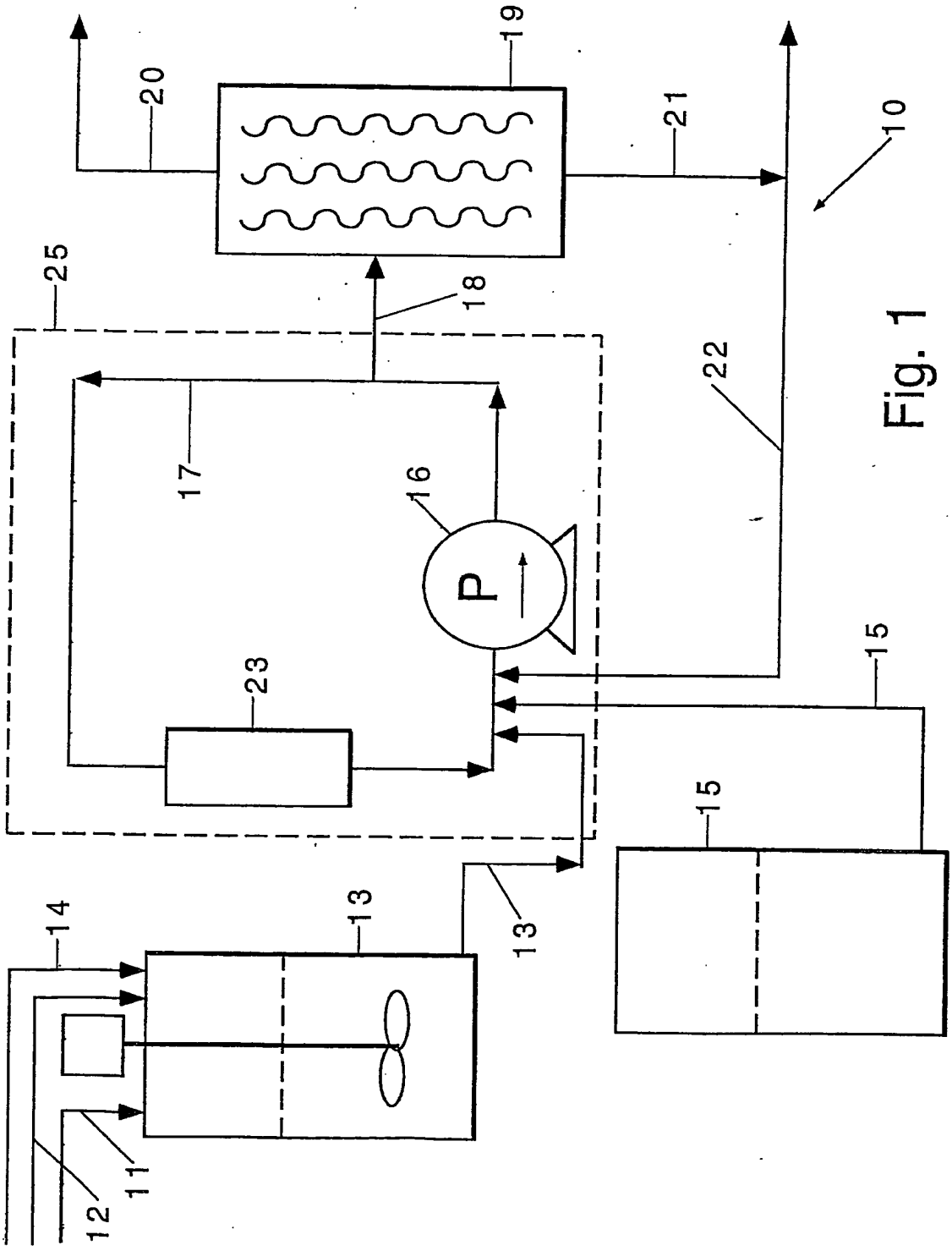

Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/27444

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 B01D9/00 B01J2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K B01D B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 14036 A (BEGON DOMINIQUE ;KOHL MICHAEL (FR); GUILLAUME PFEFER (FR); AVENTIS) 1 March 2001 (2001-03-01) the whole document	1-25
X	US 4 826 689 A (VIOLANTO MICHAEL R) 2 May 1989 (1989-05-02) the whole document	1-25
X	US 6 221 398 B1 (TROFAST JAN ET AL) 24 April 2001 (2001-04-24) the whole document	1-25
X	WO 00 38811 A (THEOPHILUS ANDREW LEWIS ;GLAXO GROUP LTD (GB); SINGH HARDEV (GB);) 6 July 2000 (2000-07-06) the whole document	1-25

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 2002	30/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hornich, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/27444

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 53282 A (CARPENTER STEPHEN THOMAS ;SMITHKLINE BEECHAM PLC (GB); SMITHKLINE) 14 September 2000 (2000-09-14) the whole document	1-25
X	WO 01 32125 A (SAVAGE ANDREW PATRICK ;GLAXO GROUP LTD (GB); FERRIE ALAN RONALD (G) 10 May 2001 (2001-05-10) the whole document	1-25
P,X	WO 02 00198 A (THEOPHILUS ANDREW LEWIS ;GLAXO GROUP LTD (GB); SINGH HARDEV (GB);) 3 January 2002 (2002-01-03) the whole document	1-25
P,X	WO 02 00200 A (THEOPHILUS ANDREW LEWIS ;GLAXO GROUP LTD (GB); SINGH HARDEV (GB);) 3 January 2002 (2002-01-03) the whole document	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/27444

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0114036 A	01-03-2001	AU	6461500 A	19-03-2001
		EP	1214129 A1	19-06-2002
		WO	0114036 A1	01-03-2001
US 4826689 A	02-05-1989	CA	2089075 A1	22-02-1992
		US	4997454 A	05-03-1991
		AU	579166 B2	17-11-1988
		AU	4501285 A	22-01-1987
		CA	1282405 A1	02-04-1991
		EP	0169618 A2	29-01-1986
		EP	0544657 A1	09-06-1993
		JP	1973762 C	27-09-1995
		JP	7002209 B	18-01-1995
		JP	62027032 A	05-02-1987
		JP	6501872 T	03-03-1994
		PT	80494 A ,B	22-11-1985
		WO	9203380 A1	05-03-1992
		AT	55921 T	15-09-1990
		DE	3579385 D1	04-10-1990
		ES	8607007 A1	01-11-1986
		IL	75250 A	31-08-1988
		NZ	212151 A	30-08-1988
US 6221398 B1	24-04-2001	AU	694863 B2	30-07-1998
		AU	5352496 A	30-10-1996
		CA	2217062 A1	17-10-1996
		CN	1186428 A	01-07-1998
		EP	0820276 A1	28-01-1998
		JP	11503448 T	26-03-1999
		NO	974557 A	02-10-1997
		NZ	305515 A	29-03-1999
		WO	9632095 A1	17-10-1996
		ZA	9602596 A	14-10-1996
WO 0038811 A	06-07-2000	AU	1877100 A	31-07-2000
		BR	9916587 A	25-09-2001
		CN	1335787 T	13-02-2002
		CZ	20012331 A3	13-03-2002
		EP	1144065 A1	17-10-2001
		WO	0038811 A1	06-07-2000
		HU	0104855 A2	29-04-2002
		JP	2002533205 T	08-10-2002
		NO	20013039 A	22-08-2001
		PL	349345 A1	15-07-2002
		TR	200101845 T2	22-10-2001
		US	6482438 B1	19-11-2002
WO 0053282 A	14-09-2000	AU	2932600 A	28-09-2000
		EP	1165197 A1	02-01-2002
		WO	0053282 A1	14-09-2000
		JP	2002538227 A	12-11-2002
WO 0132125 A	10-05-2001	AU	1160401 A	14-05-2001
		EP	1225875 A2	31-07-2002
		WO	0132125 A2	10-05-2001
		NO	20022059 A	14-06-2002
WO 0200198 A	03-01-2002	AU	6621801 A	08-01-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[redacted]tional Application No
PCT/US 02/27444

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0200198 A		WO 0200198 A1	03-01-2002
WO 0200200 A	03-01-2002	AU 6770801 A	08-01-2002
		WO 0200200 A1	03-01-2002

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C08F 218/08, 14/06, C07C 409/00 | A1

(11) International Publication Number: **WO 98/18835**

(43) International Publication Date: 7 May 1998 (07.05.98)

(21) International Application Number: PCT/EP97/05919

(22) International Filing Date: 21 October 1997 (21.10.97)

(30) Priority Data:
96203017.7 30 October 1996 (30.10.96) EP

(34) Countries for which the regional or international application was filed: NL et al.

(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL–6824 BM Arnhem (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: O, Boen Ho [NL/NL]; Koekoekstraat 14, NL–3514 CW Utrecht (NL). MALTHA, Annemarieke [NL/NL]; Zesakkers 2102, NL–6605 TG Wijchen (NL). WESTMIJZE, Hans [NL/NL]; Burgemeester Boreellaan 1, NL–7437 BB Bathmen (NL). ALFERINK, Petrus, Johannes, Theodorus [NL/NL]; Sint Anfriedlaan 4, NL–6931 GD Westervoort (NL).

(74) Agent: SCHALKWIJK, Pieter, Cornelis; Akzo Nobel N.V., Patent Dept. (Dept. APTA), P.O. Box 9300, NL–6800 SB Arnhem (NL).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROCESS TO MAKE INITIATOR COMPOSITIONS COMPRISING POLYVINYL ALCOHOL AND SURFACTANT

(57) Abstract

A process to make suspensions of thermally labile organic compounds in water is provided. The suspensions comprise at least one polyvinyl alcohol with an average degree of hydrolysis from 60 to 80 % and at least one non–ionic surfactant with an average HLB value from 14.5 to 20.0, and are suitable for use in polymerization processes. The organic compounds in the suspensions preferably have a particle size distribution where the d_{90} is less than 20 μm. The particle size distribution of the thermally labile organic compound and the specific ingredients enable the production of chemically as well as physically storage stable suspensions that combine a high compound concentration and a low viscosity. When used in vinyl chloride polymerization processes, the suspensions ensure a low fish eye level and good electrical properties, without adversely affecting the PVC's porosity and bulk density.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PROCESS TO MAKE INITIATOR COMPOSITIONS COMPRISING POLYVINYL ALCOHOL AND SURFACTANT

Introduction

The present invention relates to a process to make storage stable and low-viscous aqueous suspensions comprising thermally labile organic compounds, at least one polyvinyl alcohol, and at least one non-ionic surfactant, to suspensions that can be obtained by this process, and to the use of these suspensions in polymerization processes.

Background of the invention

Water-based suspensions are well-known as safe formulations for thermally labile organic compounds such as organic peroxides and azo-initiators. Such formulations are known for their ease of handling, allowing automation of the polymerization processes in which they are used as a source of free radicals.

US 4,039,475 and US 4,092,470 describe the preparation and use, in the polymerization of vinyl chloride monomer, of initiator suspensions which contain a combination of two non-ionic emulsifiers., viz. one with an HLB value not higher than 12.5 and one with an HLB value not lower than 12.5. The HLB value of the exemplified emulsifier combinations is below 14.0. Alternatively, one non-ionic emulsifier with an HLB value not higher than 12.5 is combined with one anionic emulsifier. The suspensions are prepared by vigorously mixing and homogenizing the components. GB-B-2 068 009 elaborates on this concept and prescribes the use of specific

ethoxylated non-ionic emulsifiers with an HLB value above 15 in combination with a non-ethoxylated non-ionic emulsifier with an HLB value below 9.

However, the early introduction and acceptance of these suspensions was hindered by production problems, their physical instability, mostly resulting in the formation of a solid cake at the bottom and a watery layer on top of the container, their effect on the polymer production process, and/or their adverse effect on the properties of the polymer made with them, particularly in polymerization processes where vinyl chloride monomer is used. For example, when formulating bis(4-tert-butylcyclohexyl) peroxydicarbonate in the way according to the prior art, we were not able to make a suspension that was storage stable, had the desired particle size distribution and an acceptable viscosity, without that the properties of poly vinyl chloride produced therewith were adversely influenced.

EP-A-0 106 627 and EP-A-0 517 290 disclose a melt-process in which a solid peroxide consecutively is slurried in water, melted, emulsified in the water, and solidified, to give a stable suspension of finely divided peroxide particles. In the process a variety of emulsifiers and protective colloids may be used. Allegedly, this process alleviates some of the problems of the earlier suspensions. However, only specific initiators, i.e. ones that allow melting without excessive decomposition, can be formulated in this way. Also, even if excessive decomposition does not occur, safety considerations may be in the way of employing this process. In order to reduce decomposition of the initiators during storage and handling, US 4,552,682 proposes to add phenolic antioxidants to chemically stabilize suspensions of peroxydicarbonates. However, such antioxidants are known to interfere with the free radicals formed in the polymerization process in

which the suspensions are used and, therefore, are typically not acceptable. Hence, the use of phenolic antioxidants cannot relieve the decomposition problems that are encountered in the process of EP-A-0 106 627 and EP-A-0 517 290.

Thus, there has been an ongoing search for a process to make improved peroxide suspensions by means of conventional milling of the solid peroxide in the presence of water. The main focus has been on improving the physical stability of the various suspensions and/or finding a solution to production problems. As a result, specific ingredients and formulations have been proposed in various documents. EP-A-0 263 619 discloses the use of specific crystalline cellulose. US 4,692,427, pertaining to suspensions of aromatic diacyl peroxides, teaches the use of magnesium aluminium silicate in combination with an alkali metal carboxymethyl cellulose. JP-A-61127701 combines a non-ionic surfactant, a colloidal protective agent, and a polyphosphoric acid alkali metal salt. JP-A-01095102 discloses a combination of PVA, gelatin or cellulose derivatives with a specific copolymer of carbon monoxide and (meth)acrylate containing anionic or cationic groups. EP-A-0 492 712 discloses the use of polyether polysiloxanes or a water-soluble copolymer of a C_8-C_{24} α-olefin and a specific α,β-unsaturated dicarboxylic acid ester in order to enable the production of finely divided peroxide dispersions. However, since the ingredients of the suspensions are not fully compatible with the polymerization process in which the suspensions are eventually used, these formulations also are generally not acceptable.

Therefore, the main disadvantage of the described suspensions of thermally labile organic compounds is that they suffer from production problems, do not fulfill storage stability requirements and/or are not

universally applicable in polymerization processes. More specifically, it is observed that some storage stable peroxide suspensions can be produced according to the prior art, but when they are used in vinyl chloride (co)polymerization, one or more properties of the resulting polymer is not acceptable.

In respect of applicability in vinyl chloride (co)polymerization processes, it is noted that current initiator suspensions have an effect on the polymer morphology, for instance porosity, the electrical properties of the polymer, and the fish eye level. Further, these initiator suspensions typically suffer from other disadvantages, such as high viscosities, which make them difficult to handle, or in some cases the suspensions cannot be milled to reduce the particle size of the organic compound. A reduction of the peroxide concentration in order to reduce the viscosity and/or the milling problems often is not acceptable from an economic point of view.

Accordingly, there still is a need for improved peroxide suspensions and an improved process to make them. More specifically, there is a need for improved, chemically and physically stable, compositions of thermally labile organic compounds which are generally applicable in polymerization processes, particularly in the polymerization process of vinyl chloride monomer. The improved compositions are to combine a high concentration of the thermally labile organic compound with an acceptable viscosity, with the thermally labile organic compound having a small average particle size, and are not to affect the properties of the polymer produced therewith. These and other objects of the present invention will be apparent from the summary and the detailed description which follow.

Summary of the invention

After many years of intensive research and development in the field of suspensions and emulsions of thermally labile organic compounds, we have now found compositions that fulfill all or most of the above-identified requirements and which can be produced by means of conventional milling techniques.

The present invention relates, in a first embodiment, to a process to prepare an aqueous suspension comprising:

- from 5 to 60% by weight of the total formulation of one or more solid thermally labile organic compounds,
- 0.5-10% by weight of the total formulation of one or more polyvinyl alcohols having an average degree of hydrolysis from 60 to less than 80%, with the proviso that no polyvinyl alcohol with a degree of hydrolysis of less than 55% is employed
- 0.05 to 1% by weight of the total formulation of one or more emulsifiers having an average HLB value from 14.5 to 20.0,

wherein at least one solid thermally labile organic compound is milled in water.

The present invention, in a second embodiment, relates to suspensions of bis(4-tert-butylcyclohexyl) peroxydicarbonate, dimyristyl peroxydicarbonate and/or lauric peracid that are obtainable by said process.

In a further embodiment, the invention relates to a process for the polymerization of vinyl chloride alone or in admixture with up to 40 weight percent of one or more ethylenically unsaturated monomers copolymerizable therewith, oligomers or (co)polymers of the

aforementioned monomers, and mixtures of one or more of the monomers, oligomers, and (co)polymers, characterized in that a peroxidic polymerization initiator and/or chain transfer agent is used in the form of an aqueous suspension as set forth above.

These and other aspects will be discussed in more detail in the following description and examples.

Detailed description of the invention

According to the first aspect of the present invention a process is provided to prepare aqueous suspensions of thermally labile organic compounds by milling and/or homogenizing the solid peroxide in an aqueous medium preferably comprising one or more particular protective colloids or one or more emulsifiers. More preferably, the aqueous medium comprises one or more particular protective colloids and one or more emulsifiers. The term "thermally labile organic compound," as used in this specification, defines compounds that will form free radicals upon thermal decomposition. This class of compounds encompasses organic peroxides, azo-initiators, C-C initiators, NO-compounds, and peroxycarboxylic acids. Preferred compounds for use in the present invention are organic peroxides and azo-initiators. More preferred are organic peroxides.

More particularly, preferred organic peroxides for use in the present invention are diacyl peroxides, peracids, and peroxydicarbonates. More preferred are peroxides selected from dicyclohexyl peroxydicarbonate, bis(4-tert-butylcyclohexyl) peroxydicarbonate, dimyristyl peroxydicarbonate, dicetyl peroxydicarbonate, didecyl peroxydicarbonate, didecanoyl peroxide,

dilauroyl peroxide, lauric peracid, and mixtures thereof. More preferred still are suspensions of bis(4-tert-butylcyclohexyl) peroxydicarbonate, dimyristyl peroxydicarbonate, and/or lauric peracid. The most preferred organic peroxide formulated according to the invention is bis(4-tert-butylcyclohexyl) peroxydicarbonate. This particular peroxide shows an unacceptable thermal decomposition rate when melted and cannot be processed or formulated in ways involving a melting step. However, also for the other preferred compounds the process according to the invention, where the peroxide is milled/homogenized in the solid state, is preferred from a safety point of view.

The amount of thermally labile organic compounds to be used in the process to make the aqueous suspension usually falls in the range of 5-60% by weight, based on the weight of the suspension. Preferably, 20-50% by weight of the compound is present. Most preferred are concentrated suspensions where the thermally labile organic compound is present in a concentration of 35-50% by weight. At concentrations of less than 5% by weight the cost of transportation becomes prohibitive and at concentrations above 60% by weight the products cannot be handled easily and may even be unsafe.

The storage stability of the suspension made in the process according to the invention, preferably is greater then 2 months, more preferably more than 3 months.

The Brookfield viscosity of the suspension that is made in the process according to the invention, preferably is between 750 to 5000 mPa.s, more preferably between 750 and 3750 mPa.s. More preferably still, such a Brookfield viscosity is combined with an Erichsen viscosity from 50 to 250

mPa.s. Most preferred are suspensions with a Brookfield viscosity from 1000 to 2500 mPa.s and an Erichsen viscosity from 70 to 150 mPa.s.

The particle size of the thermally labile organic compound in the suspension is preferably very small, in order to obtain all desired properties of both the suspension and the polymers prepared in processes where the suspension is used. Therefore, the d_{90} of the particle size distribution is preferably less than 20 μm. More preferred are suspensions where the organic compound has a particle size distribution with a d_{90} within the range of 0.1-15 μm. The most preferred suspensions are characterized by a d_{90} below 10 μm.

In the process according to the invention, use is made of an aqueous medium in which the thermally labile organic compound is dispersed. This aqueous medium preferably comprises from 0.5 to 20% by weight of at least one specific polyvinyl alcohol as the protective colloid (based on the total weight of the suspension). More preferably, the colloid makes up 1 to 10% by weight, most preferably from 1 to 5% by weight, of the total formulation.

More particularly, the specific polyvinyl alcohols (PVAs) that can be used in the compositions according to the invention are saponified polyvinyl acetates with a degree of hydrolysis of between 60 and 80%. Preferably, the degree of hydrolysis of the PVA is from 62 to 78%. If more than one PVA is used, the indicated degree of hydrolysis is generally the weight averaged degree of hydrolysis of the products used, with the proviso that all PVA must have a degree of hydrolysis greater than 55%. Although the PVAs may be combined with other known colloids, it is preferred to use the referenced PVAs exclusively.

The emulsifiers used in the compositions that can be produced according to the present invention are characterized by their HLB value being from 14.5 to 20.0. The HLB value is indicative of the hydrophilic-lipophilic balance, as described in "The Atlas HLB-system, a time saving guide to emulsifier selection" published by Atlas Chemical Industries Inc., 1963. For blends of emulsifiers the HLB value is the weight average HLB value of the components. Preferably, emulsifiers with an HLB value from 15.7 to 20.0 are used. More preferred are emulsifiers with an HLB value from 16.9 to 20.0. More preferred still are emulsifiers with an HLB value from 17.8 to 20.0. Most preferred are fatty alcohol ethoxylates and fatty ester ethoxylates with an HLB value in the indicated range. Less preferred emulsifiers are the ethoxylated sorbitan esters since they often lead to problems in respect of the storage stability of the suspension. Typically, the emulsifiers are used in a concentration less than 1% by weight of the total formulation. Preferred are emulsifier concentrations from 0.05 to 0.8 % by weight of the total formulation.

In the process according to the invention, the aqueous medium may further comprise one or more thickeners in a concentration up to 2% by weight of the total formulation. Preferably, the thickener makes up less than 1% by weight of the suspension. Non-limiting examples of thickeners useful in the formulation are xanthane gum, Arabic gum, and alginates.

Further, other standard additives, including pH-adjusting agents such as calcium oxide or phosphate buffers, sequestering agents, and, if desired, biocides, e.g. fungicides, can be used. The concentration of these additives will depend on the desired effect and the other ingredients in the suspension. Given the information presented here, the skilled man will

have no problem in selecting appropriate concentrations of the individual ingredients in the suspension of choice.

All of the ingredients listed above preferably are part of the aqueous medium in which the solid thermally labile organic compound is dispersed. However, one or more of the ingredients may also be added after the dispersion step of the thermally labile organic compound. In that case, it is preferred to make a suspension with a higher than desired concentration of the thermally labile organic compound(s) which is then subsequently diluted with a concentrated solution of the required ingredient.

The temperature of the aqueous medium prior to the milling/homogenization step is preferably below the lowest recommended storage temperature of the solid thermally labile organic compound(s) being dispersed. More preferably, the processing temperature is between 0 and 15°C. Most preferred is a temperature between 0 and 5°C. Lower temperatures are not very economical and may call for the use of undesired anti-freeze agents, while higher temperatures can result in undesired decomposition of the initiator.

The primary advantage of the present invention is that it provides a process to make chemically and physically stable, low viscous, concentrated suspensions of a thermally labile organic compound with a small average particle size and a good particle size distribution, which can be used in vinyl chloride polymerizations without affecting the electrical properties of the polymer. Preferred suspensions of said thermally labile organic compound mainly contain one or more PVAs as the protective colloid and minor quantities of one or more non-ionic emulsifiers. Therefore, the suspensions of the present invention do not adversely affect polymerization processes

or any property of the resultant polyvinyl chloride (PVC). These suspensions can actually improve properties such as the fish eye level and the morphology of the resultant polymer. Hence, the suspensions according to the present invention enable the use of polymerization initiators which are efficient, easy to handle, and have a favourable effect on the polymer produced with them.

The process involves, preferably, a first mixing step in which the thermally labile organic compound is stirred into an aqueous medium comprising emulsifier(s) and protective colloid(s) to form a mixture; this mixture preferably is then milled to form a coarse suspension, after which, preferably, the compound is more finely divided by further milling or homogenization. If and when a thickener, pH stabilizer or other ingredient is used in the formulation, it may be added at any point in the production process. Preferably, such an ingredient is added in the form of a concentrated solution.

The mixing step only requires the use of a stirrer of any conventional type. For the step to form the coarse suspension typically use is made of a high shear mixer, for instance a colloid mill, high-shear rotor-stator mixers, high-speed pump, etc.. Milling the coarse dispersion to further reduce the particle size of the thermally labile organic compound can be done by any equipment that is able to induce still higher shear forces, or by impact mills. Examples of such suitable equipment include, high-frequency and ultrasonic oscillators, perl mills, roller mills, and homogenizers. Given that concentrated suspensions with partially saponified polyvinyl acetate were typically found to form a thick paste during milling, it is surprising and unexpected that such a milling process can be carried out in a convenient way on the concentrated suspensions of the present invention.

In a second embodiment, the invention relates to suspensions of bis(4-tert-butylcyclohexyl) peroxydicarbonate, dimyristyl peroxydicarbonate and/or lauric peracid that are obtainable by the above-mentioned process. Most preferred are suspensions of bis(4-tert-butylcyclohexyl) peroxydicarbonate. Until now, these suspensions could not be produced without substantial decomposition (in a melting process) or without a concentrated, low-viscous, storage stable suspension with small particle size being formed (milling process), or without the properties, such as morphology or electrical conductivity, of the polymer produced being adversely influenced.

The present invention also relates to a polymerization process where at least one of the above-described suspensions is used as (one of) the polymerization initiator(s) and/or chain transfer agent(s) in the polymerization of vinyl chloride alone or in admixture with up to 40 weight percent of one or more ethylenically unsaturated monomers copolymerizable therewith, oligomers and (co)polymers of the aforementioned monomers, and mixtures of two or more of these monomers, oligomers, and polymers. The use of these suspensions is further detailed below.

The polymerizable monomers for the present polymerization process include vinyl halides, particularly vinyl chloride, and ethylenically unsaturated monomers having at least one terminal unsaturated group. Examples of such ethylenically unsaturated monomers include esters of acrylic acid such as methyl acrylate, ethyl acrylate, butyl acrylate, octyl acrylate, cyanoethyl acrylate, and the like, esters of methacrylic acid such as methyl methacrylate, butyl methacrylate, and the like, styrene and styrene derivatives including α-methylstyrene, vinyl toluene, chlorostyrene

and the like, acrylonitrile, ethyl vinyl benzene, vinyl acetate, vinyl naphthalene, etc., and di-olefins including, but not limited to, butadiene, isoprene, chloroprene, and the like, and other ethylenically unsaturated monomers known to those of ordinary skill in the art.

In addition, oligomers and polymers made from one or more of the above-identified monomers may also be reacted with other monomers, polymers or oligomers in the present polymerization process. Of course, mixtures of two or more of the polymerizable materials can be used. In all cases there will be at least 60% of vinyl chloride monomer, oligomer or polymer in the polymerizable mixture.

Generally, a polymerizable composition comprises 0.01-6.0% by weight of one or more thermally labile organic compounds (initiators), based on the polymerizable monomers, and when polymerizing vinyl chloride alone, preferably 0.01-0.3% by weight of the initiator, based on the monomer. If one or more of the initiators are in the form of a composition according to the invention, the amount of the composition is to be chosen such that the indicated amount of pure initiator is supplied. When peracid suspensions according to the invention are used as an initiator, a chain transfer agent or as a combined initiator and chain transfer agent in a vinyl chloride polymerization process, such suspensions may also be combined with the aforesaid initiator suspensions. Chain transfer agents are typically employed in a concentration of between 0.001 and 10.0% by weight of pure chain transfer agent, based on the polymerizable materials. Preferably, from 0.01 to 1% by weight of these chain transfer agents is used.

A significant advantage of the present process for the polymerization of vinyl chloride is that the use of suspensions of the present invention leads to greater flexibility in the polymerization process itself. More particularly, when the present solid peroxide compositions according to the state of the art are used in vinyl chloride polymerization, the peroxide composition must be added to the polymer before the mixture is brought to the polymerization temperature in order to avoid adverse effects, such as increased fish eye levels, on the properties of the resultant polymer. However, in the process of the present invention, the polymerization initiator may be added to the vinyl chloride monomer after it is heated to the polymerization temperature or may even be dosed stepwise or gradually during the polymerization reaction. These features provide greater flexibility in the polymerization process as well as a means of gaining better control over the process and the products of the process.

The polymerization process of the present invention typically is a suspension polymerization process in which an aqueous dispersion of vinyl chloride monomer and the polymerization initiator are heated to cause polymerization of the monomer as a result of free radical decomposition of the polymerization initiator. However, the suspensions obtainable by the process according to the invention can also be used in a so-called "mass polymerization" process. The polymerization conditions employed are the conventional conditions for vinyl chloride monomer polymerization. For a detailed description of the process conditions, as well as the types of monomers which can be polymerized by this method, reference may be made to US 3,825,509, which is incorporated herewith by reference.

The present polymerization process, however, may differ slightly from that of US 3,825,509 in that it is not necessary to add the ingredients to the polymerization reactor in the order of water, dispersant, polymerization initiator, and, finally, monomer. While this conventional methodology is within the scope of the present invention, the present invention also encompasses reactions where the water, the dispersing agent, and the monomers are added to the reactor and heated to the polymerization temperature prior to the introduction of the polymerization initiator. In such reactions the polymerization initiator is added all at once, gradually or stepwise during the polymerization process.

Previously, it was considered disadvantageous to add a solid polymerization initiator at the reaction temperature, since the fish eye level would then increase to unacceptable levels. In the examples which follow it is demonstrated that the present suspensions do not significantly increase the fish eye level. Furthermore, dosing at reaction temperature may allow a better control of the polymerization rate in the polymerization process.

The polymerization process according to the invention results in polymers which exhibit desirable properties, including better electrical properties, lower fish eye levels, and, in some instances, improved polymer morphology, such as porosity.

The following examples are provided to further illustrate the present invention and are not to be interpreted as limiting the invention in any way.

Experimental

Materials:

The following PVAs were used:

Polyviol® M05/190 ex Wacker (approx. 82.5% hydrolysis)

Gohsenol® KH20 ex Nippon Gohsei (approx. 80% hydrolysis)

Polyviol® V03/240 ex Wacker (approx. 77% hydrolysis)

Gohsenol® KP08 ex Nippon Gohsei (approx. 73% hydrolysis)

Alcotex® 72.5 ex Harco (approx. 72.5% hydrolysis)

Ethapol® 66 ex CIRS (approx. 66% hydrolysis, microemulsion)

Polyvic® SP808 ex 3V (approx. 65% hydrolysis)

Unitika® UMR10M ex Unitika Chemical (approx. 65% hydrolysis)

Alcotex® 552P ex Harco (approx. 55.5% hydrolysis)

Gohsenol® LL02 ex Nippon Gohsei (approx. 48% hydrolysis)

The following non-ionic emulsifiers were used:

Berol® 08 ex Berol Nobel (HLB = 18.7)

Igepal® CO897ex GAF (HLB = 17.8)

Brij® 35 ex ICI (HLB = 16.9)

Brij®58 ex ICI (HLB = 15.7)

Cedepal® E710 ex Domtar (HLB = 14.4)

Elfapur® T110 ex Akzo Nobel (HLB = 13.5)

The thickener employed was a xanthane gum, Rhodigel® 23, supplied by Rhone Poulenc.

Bis(4-tert-butylcyclohexyl) peroxydicarbonate (Perkadox® 16), dicetyl peroxydicarbonate (Liladox® 90P) and dimyristyl peroxydicarbonate (Perkadox® 26) were supplied by Akzo Nobel and used as an initiator.

VCM was of polymerization grade, while all other materials were standard chemicals of reagent grade. These compounds were used without further purification.

Procedures:

1. Suspensions were prepared by mixing the thermally labile organic compound in the aqueous phase containing the other ingredients in the proper ratio, with a turbine-type stirrer, at 10°C. Subsequently, the mixture was first dispersed with an Ultra-Turrax® rotor-stator dissolver for 5 minutes at 700 W stirring energy per kg of mixture, to form coarse suspensions and next milled with a 500 ml Drais® Perl Mill PM1. The perl mill was filled with 1-2 mm glass beads for 80% by volume. The coarse suspensions were milled at a rate of 400 ml/min at a temperature of 10°C maximum, preferably 5°C. Finally, the suspensions were deaerated.

2. The suspensions were characterized in terms of viscosity, particle size (distribution), and physical stability on aging (separation). The viscosity was determined with an Erichsen® Viscometer, type 332-1 and a Brookfield® LVT viscometer at 12 rpm, spindle 3. The particle size (distribution) was determined by light scattering techniques using a Malvern® Particle Sizer M3. Separation of the suspensions was determined visually by storing in 500 ml HDPE jars.

3. The polymerization reactions were carried out in a one-litre Büchi stainless steel autoclave with stirrer and baffle. The reactor was filled with aqueous protective colloid solution in which the phosphate buffer was dissolved. Depending on the tests to be performed (see below), one of the following methods was used:

3.1 A suspension of the thermally labile organic compound was added in an amount of 0.07% pure peroxide, based on the vinyl chloride monomer. The reactor was then evacuated and flushed with nitrogen four times while stirring. After addition of the VCM, the mixture was heated to reaction temperature (53.5°C) in 60 minutes.

3.2 The reactor was evacuated and flushed with nitrogen four times while stirring. Then VCM was mixed in at room temperature and the reaction mixture was heated, in 25 minutes, to 53.5°C. Subsequently, the suspension of the thermally labile organic compound was added in an amount of 0.07% pure peroxide, based on the vinyl chloride monomer, by means of an appropriate syringe through a septum.

For both methods the reactor was cooled after 6 hours of polymerization time and excess vinyl chloride monomer was vented. The polyvinyl chloride was filtered, washed, dried overnight at 50°C, weighed, and analyzed. The conversion of the vinyl chloride monomer was determined by gravimetric analysis.

4. The DOP porosity and the volume resistivity of the PVC were determined by analyzing material from method 3.1, in accordance with DIN 53417 (centrifuge method) and ASTM D257-66 (22°C, 46% R.H.), respectively.

5. The fish eye level, particle size (distribution), and bulk density were analyzed in conventional ways on PVC obtained by method 3.2.
The fish eye level was determined in accordance with the method of O. Leuchs, Kunststoffe, 50(4) 1960, pp. 227-234. Preferably, the fish eye level is as low as possible. The polyvinyl chloride mean particle size was determined with a Coulter Counter® (multisizer), and the bulk density was determined in a conventional way by means of an Erichsen DIN cup 243/11.8.

Example 1

A suspension was prepared containing 2% by weight of Alcotex 72.5 (approx. hydr. 72.5%), 0.3% by weight of Igepal CO897 (HLB 17.8), 0.15% by weight of xanthane gum, 0.05% by weight of CaO, 40% by weight of Perkadox 16, the remainder being demineralized water.

The suspension showed excellent physical and chemical stability during more than 3 months of storage and had the following properties:

d_{50} (μm)	5
d_{90} (μm)	12
Erichsen viscosity (mPa•s)	140
Brookfield viscosity (mPa•s)	1530

The PVC produced using this suspension had the following properties:

DOP porosity (%)	22
vol.resistivity (Ωcm)	$14 \cdot 10^{13}$
fish eyes (m^{-2})	30
average particle size (μm)	160
bulk density ($g \cdot ml^{-1}$)	0.40

Example 2

Example 1 was repeated, except that Polyviol V03/240 (approx. hydr. 78%) was substituted for the Alcotex 72.5 and 0.4% of Berol 08 (HLB 18.7) was used instead of the 0.3% Igepal CO897. The suspension had the following properties:

d50 (μm)	4.8
d90 (μm)	10.5
Erichsen viscosity (mPa•s)	160
Brookfield viscosity (mPa•s)	4950.

The suspensions were storage stable for at least 3 months.

Example 3

A suspension was prepared containing 2% by weight of Unitika UMR10m (approx. hydr. 65%), 0.3% by weight of Berol 08 (HLB 18.7), 0.15% by weight xanthane gum, 0.05% by weight CaO, 40% by weight of Perkadox 16, the remainder being demineralized water.

The suspension showed excellent physical and chemical stability during more than 6 months of storage and had the following properties:

d_{50} (μm)	4
d_{90} (μm)	9
Erichsen viscosity (mPa•s)	130
Brookfield viscosity (mPa•s)	1800

The PVC produced using this suspension had the following properties:

DOP porosity (%)	24
vol.resistivity (Ωcm)	$12 \cdot 10^{13}$
fish eyes (m^{-2})	25
average particle size (μm)	155
bulk density ($g \cdot ml^{-1}$)	0.40

Example 4

A suspension was prepared containing 1.5% by weight of Polyvic SP808 (approx. hydr. 65%), 0.6% by weight of Brij 35 (HLB 16.9), 0.15% by weight xanthane gum, 0.05% by weight CaO, 40% by weight of Perkadox 16, the remainder being demineralized water.

The suspension had the following properties:

Erichsen viscosity (mPa•s)	170
Brookfield viscosity (mPa•s)	4120

The product was storage stable for at least 3 months.

Comparative Example A

Example 1 was repeated, except that this time the suspension consisted of 1.5% by weight of Gohsenol KP08 (approx. hydr. 73%), 0.15% by weight of xanthane gum, 0.05% by weight of CaO, 40.0% by weight of Perkadox 16, and 58.25% by weight of water, with the following results.

The suspension was physically and chemically stable during less than 8 weeks of storage and had the following properties:

d_{50} (µm)	6
d_{90} (µm)	19
Erichsen viscosity (mPa•s)	220
Brookfield viscosity (mPa•s)	3600

The PVC produced using this suspension had the following properties:

DOP porosity (%)	22
vol.resistivity (Ωcm)	$15 \cdot 10^{13}$
fish eyes (m^{-2})	> 5,000
average particle size (µm)	145
bulk density ($g \cdot ml^{-1}$)	0.40

Comparative Example B

Example 1 was repeated, except that Alcotex 552P (average hydrolysis 55.5% but with a substantial amount of material with a degree of hydrolysis below 55%) was substituted for the Alcotex 72.5 and the Igepal CO897 was replaced with Berol 08 (HLB 18.7).
The resulting suspension was very thixotropic and showed unacceptable storage and handling properties.

Comparative examples C and D

Example 3 was repeated, except that the Berol 08 was replaced with Cedepal E710 (HLB 14.4) and Elfapur T110 (HLB 13.5) in Examples C and D, respectively. Both suspensions were too thick to be handled easily.

Comparative Example E

Example 3 was repeated, except that 1% by weight of Gohsenol LL02 (approx. hydr. 48%) and 1% by weight of Polyviol M05/190 (approx. hydr. 82.5%) were substituted for the 2% by weight of Unitika UMR10m.
The resulting suspension was not storage stable. After two weeks it was too thick to be handled easily.

Comparative Example F

Example 1 was repeated, except that Gohsenol KH20 (approx. hydr. 80%) was substituted for the Alcotex 72.5. This suspension was too thick to be processable. No representative sample was attainable.

Comparative Example G

Example 3 was repeated, except that Ethapol 66 (approx. hydr. 66%) was substituted for the Unitika UMR10m. The Ethapol is a mixture of PVAs with low (46%) and high (>76%) degrees of hydrolysis.
This suspension was too thick to be handled easily.

Examples 5-6

The experiment of Example 1 was repeated, except that the Igepal CO897 was replaced with another non-ionic emulsifier, as indicated in the following table.

Example	Non-ionic emulsifier	HLB value	Erichsen visc. (mPa•s)	Brookfield (mPa•s)
5	Brij 35	16.9	120	1350
6	Brij 58	15.7	160	1820

The products were storage stable.

Example 7

A suspension was prepared according to procedure 1, using 40% by weight of Perkadox 26, 2.0% by weight of Alcotex 72.5, 0.3% by weight of Berol 08, 0.17% by weight of xanthane gum, and 57.53% by weight of water.

The suspension showed excellent physical and chemical stability during more than 3 months of storage and had the following properties:

d_{50} (μm)	8.6
d_{90} (μm)	20.0
Erichsen viscosity (mPa•s)	90
Brookfield viscosity (mPa•s)	1920

Example 8

A suspension was prepared according to procedure 1, using 44.44% by weight of Liladox® 90P (equivalent to 40% by weight of dicetyl peroxydicarbonate), 2.0% by weight of Unitika UMR 10M, 0.7% by weight of Berol 08, 0.15% by weight of xanthane gum, 0.08% by weight of sodium dicarbonate, and 52.63% by weight of water.

The suspension showed good physical and chemical stability during more than 3 months of storage, and had the following properties:

d_{50} (μm)	5.3
d_{90} (μm)	19.9
Erichsen viscosity (mPa•s)	75
Brookfield viscosity (mPa•s)	1630

Claims

1. A process to prepare an aqueous suspension comprising:
- from 5 to 60% by weight of the total formulation of one or more solid thermally labile organic compounds,
- 0.5-10% by weight of the total formulation of one or more polyvinyl alcohols having an average degree of hydrolysis from 60 to less than 80%, with the proviso that no polyvinyl alcohol with a degree of hydrolysis of less than 55% is employed
- 0.05 to 1% by weight of the total formulation of one or more emulsifiers having an average HLB value from 14.5 to 20.0,
wherein at least one solid thermally labile organic compound is milled in water.

2. A process according to claim 1, wherein at least one solid thermally labile organic compound is milled in an aqueous medium, which medium comprises at least one of said polyvinyl alcohols or at least one of said emulsifiers.

3. A process according to claim 1 or 2, wherein the thermally labile organic compound is selected from diacyl peroxides, peracids, peroxydicarbonates, and mixtures thereof.

4. A process according to claim 3, wherein the thermally labile organic compound is dicyclohexyl peroxydicarbonate, bis(4-tert-butylcyclohexyl) peroxydicarbonate, dimyristyl peroxydicarbonate, dicetylperoxy peroxydicarbonate, didecyl peroxydicarbonate, didecanoyl peroxide, dilauroyl peroxide, or lauric peracid, or a mixture of two or more of these compounds.

5. A process according to any one of claims 1-4, wherein the particle size distribution of the thermally labile organic compound in the final suspension has a d_{90} of less than 20μm.

6. A process according to claim 5, wherein the particle size distribution of the thermally labile organic compound in the suspension has a d_{90} of less than 15μm.

7. A process according to any one of the preceding claims, wherein the degree of hydrolysis of the polyvinyl alcohol is from 62 to 78%.

8. A process according to any one of the preceding claims, wherein the emulsifier has an average HLB value from 16.9 to 20.0.

9. A process according to any one of the preceding claims wherein the concentration of the thermally labile organic compound is from 35 to 45% by weight, the concentration of the polyvinyl alcohol is from 1 to 5% by weight, and the concentration of the emulsifier is from 0.05 to 0.8% by weight, all based on the total weight of the formulation.

10. A process according to any one of the preceding claims, wherein the final suspension further comprises a thickener in a concentration up to 2% by weight of the total formulation.

11. A process according to any one of the preceding claims, wherein the final suspension further comprises one or more additives selected from pH-adjusting agents, sequestering agents, and biocides.

12. A process according to any one of the preceding claims, wherein the process involves a mixing step and at least one milling step during which the temperature is controlled, preferably at a temperature below 10°C.

13. A suspension of bis(4-tert-butylcyclohexyl) peroxydicarbonate, dimyristyl peroxydicarbonate, lauric peracid, or a mixture thereof, obtainable by a process according to any one of claims 1-12.

14. A suspension according to claim 13 comprising bis(4-tert-butylcyclohexyl) peroxydicarbonate as the sole thermally labile organic compound.

15. A polymerization process wherein vinyl chloride, optionally together with up to 40% by weight of ethylenically unsaturated comonomers, is polymerized using one or more thermally labile organic compounds, characterized in that an aqueous suspension is used that is obtainable by the process as defined in any one of claims 1-12.

16. A polymerization process according to claim 15, characterized in that an aqueous suspension is used comprising just bis(4-tert-butylcyclohexyl) peroxydicarbonate as the thermally labile organic compound.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 97/05919

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08F218/08 C08F14/06 C07C409/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08F C09J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 492 712 A (AKZO NV) 1 July 1992 cited in the application * see examples 4-6 ; page 6, line 3 * see page 3, line 15 - page 4, line 31; examples 1-3,7-23	1-16
X	GB 2 068 008 A (KENOGARD AB) 5 August 1981 * see page 2, line 13-53 ; examples 1-6 ; page 1, line 50 - page 2, line 12 * see page 3, line 59 - page 4, line 5	1-4,7-16
X	EP 0 385 734 A (SUMITOMO CHEMICAL CO) 5 September 1990 * abstract * see column 2, line 39 - column 3, line 34; examples 1-12	1,2,5-9, 11,12,15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 1998	16/03/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hammond, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 97/05919

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 068 009 A (KENOGARD AB) 5 August 1981 cited in the application see examples 1-6	1-4,7-16
Y	EP 0 279 384 A (AIR PROD & CHEM) 24 August 1988 cited in the application see page 3, line 18-27	1-16
Y	EP 0 517 290 A (BEROL NOBEL AB) 9 December 1992 see examples 13,14	1-16

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 97/05919

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0492712 A	01-07-92	CA 2058347 A	25-06-92
		JP 4318002 A	09-11-92
GB 2068008 A	05-08-81	SE 435844 B	22-10-84
		AU 522909 B	01-07-82
		BE 887249 A	27-07-81
		CA 1160618 A	17-01-84
		CH 644135 A	13-07-84
		DE 3102781 A	04-02-82
		FI 810214 A	29-07-81
		FR 2474509 A	31-07-81
		JP 56110703 A	02-09-81
		JP 58051002 B	14-11-83
		NL 8100378 A,C	17-08-81
		SE 8000669 A	29-07-81
		US 4499250 A	12-02-85
		US 4547481 A	15-10-85
EP 0385734 A	05-09-90	JP 1929945 C	12-05-95
		JP 2289640 A	29-11-90
		JP 6055874 B	27-07-94
		DE 69011157 D	08-09-94
		DE 69011157 T	08-12-94
		US 5070134 A	03-12-91
		US 5110856 A	05-05-92
GB 2068009 A	05-08-81	SE 435843 B	22-10-84
		AU 522636 B	17-06-82
		AU 6663081 A	27-08-81
		BE 887248 A	27-07-81
		CA 1161024 A	24-01-84
		CH 644134 A	13-07-84
		DE 3102770 A	17-12-81
		FI 810213 A	29-07-81
		FR 2474510 A	31-07-81
		JP 1217221 C	17-07-84
		JP 56110702 A	02-09-81
		JP 58051001 B	14-11-83
		NL 8100377 A,B,	17-08-81
		SE 8000668 A	29-07-81

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern... al Application No
PCT/EP 97/05919

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2068009 A		US 4415716 A	15-11-83
EP 0279384 A	24-08-88	US 4921898 A	01-05-90
		CA 1322064 A	07-09-93
		DE 3852325 D	19-01-95
		DE 3852325 T	27-04-95
		JP 2624741 B	25-06-97
		JP 63223053 A	16-09-88
EP 0517290 A	09-12-92	AU 639857 B	05-08-93
		AU 1712692 A	11-03-93
		CS 9201599 A	16-12-92
		DE 69202819 D	13-07-95
		DE 69202819 T	21-12-95
		ES 2074810 T	16-09-95
		JP 2529632 B	28-08-96
		JP 5178921 A	20-07-93
		JP 2704863 B	26-01-98
		JP 8104707 A	23-04-96
		NO 179554 B	22-07-96
		SE 9101674 A	01-12-92
		US 5403804 A	04-04-95
		US 5574200 A	12-11-96
		US 5270271 A	14-12-93